



King's Research Portal

DOI:

[10.1210/jc.2017-01235](https://doi.org/10.1210/jc.2017-01235)

Document Version

Publisher's PDF, also known as Version of record

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Melvin, A., Adams, C., Flanagan, C., Gaff, L., Gratton, B., Gribble, F., Roberts, G., Semple, R. K., O'Rahilly, S., Rubino, F., Stears, A., & Savage, D. B. (2017). Roux-en-Y Gastric Bypass Surgery in the Management of Familial Partial Lipodystrophy Type 1. *The Journal of clinical endocrinology and metabolism*, 102(10), 3616-3620. <https://doi.org/10.1210/jc.2017-01235>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Roux-en-Y Gastric Bypass Surgery in the Management of Familial Partial Lipodystrophy Type 1

Audrey Melvin,^{1,2} Claire Adams,^{1,2} Catherine Flanagan,¹ Lisa Gaff,¹ Barbara Gratton,¹ Fiona Gribble,² Geoffrey Roberts,² Robert K. Semple,^{1,2} Stephen O'Rahilly,^{1,2} Francesco Rubino,³ Anna Stears,¹ and David B. Savage^{1,2}

¹National Severe Insulin Resistance Service, Addenbrooke's Hospital, Cambridge CB2 0QQ, United Kingdom;

²Metabolic Research Laboratories, Wellcome Trust-Medical Research Council Institute of Metabolic Science, University of Cambridge, Cambridge CB2 0QQ, United Kingdom; and ³Bariatric and Metabolic Surgery, Division of Diabetes and Nutritional Sciences, King's College London, London SE5 9NU, United Kingdom

Context: Familial partial lipodystrophy type 1 (FPLD1) is an extreme form of central adiposity, with peripheral lipodystrophy associated with severe manifestations of the metabolic syndrome, often poorly responsive to standard therapeutic approaches. Body mass index in FPLD1 varies but, in many cases, is below the level at which metabolic surgery is usually considered as a therapeutic option.

Design: We detailed the metabolic response to gastric bypass surgery of three patients with FPLD1, refractory to medical therapy.

Results: Roux-en-Y gastric bypass (RYGB) was associated with weight loss and substantial improvements in glycemic control and insulin sensitivity. All three patients were able to stop using insulin. Glucose tolerance testing in one patient demonstrated an increase in L-cell-derived gut hormone responses postoperatively.

Conclusion: RYGB surgery substantially improved glycemic control in three patients with FPLD1, two of whom had body mass indices below 30 kg/m². RYGB should be considered in patients with partial lipodystrophy and refractory metabolic disease. (*J Clin Endocrinol Metab* 102: 3616–3620, 2017)

Familial partial lipodystrophy type 1 (FPLD1) is characterized by central fat accumulation, reduced peripheral subcutaneous adipose tissue, and ectopic fat deposition (1). The metabolic sequelae of FPLD1 can be severe and include insulin-resistant type 2 diabetes, dyslipidemia, nonalcoholic fatty liver disease (NAFLD), and hyperandrogenism. Patients with FPLD1 have long posed a treatment challenge, with current approaches targeting metabolic complications of ectopic fat deposition using similar strategies to those used in obese patients with diabetes (2). Recombinant leptin therapy is very effective in patients with generalized lipodystrophy and to a lesser extent in other forms of partial lipodystrophy, but

leptin levels in most patients with FPLD1 are well above current thresholds (4 to 10 µg/L) for leptin therapy (3). Here we report on the metabolic outcomes of gastric bypass surgery in three patients with FPLD1.

Materials and Methods

Participants were assessed at the National Severe Insulin Resistance Service, Cambridge University Hospital, and further evaluated at the National Institute for Health Research/Wellcome Trust Clinical Research Facility. Ethical approval was obtained from the East of England-Cambridge Research Ethics Committee, and participants have consented to the use of data for scientific publication. Dual-energy X-ray absorptiometry (DEXA) imaging was undertaken on Lunar iDXA or

ISSN Print 0021-972X ISSN Online 1945-7197

Printed in USA

This article has been published under the terms of the Creative Commons Attribution License (CC BY; <https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. Copyright for this article is retained by the author(s).

Received 31 May 2017. Accepted 21 July 2017.

First Published Online 26 July 2017

Abbreviations: BMI, body mass index; DEXA, dual-energy X-ray absorptiometry; FPLD1, familial partial lipodystrophy type 1; GLP-1, glucagonlike peptide-1; HbA_{1c}, hemoglobin A_{1c}; LMNA, lamin A/C; NAFLD, nonalcoholic fatty liver disease; PLIN1, perilipin 1; PPARG, peroxisome proliferator activated receptor γ; PYY, peptide YY; RYGB, Roux-en-Y gastric bypass.

Lunar Prodigy (GE Health Care), with specialized assays completed at the Core Biochemical Assay Laboratory, University of Cambridge.

Results

Patient A

A 49-year-old female attending the National Severe Insulin Resistance Service had originally presented at age 32 years with gestational diabetes, which persisted postpartum. She developed central adiposity during puberty. She has a positive family history for diabetes (Supplemental Fig. 1). Prior to referral, her glycemia had been managed with metformin (stopped due to gastrointestinal intolerance) and gliclazide, followed by insulin therapy and exenatide. Examination and DEXA imaging (Supplemental Fig. 2) confirmed central adiposity with

peripheral lipodystrophy. Biochemical tests were consistent with those typical of patients with partial lipodystrophy. Therefore, having excluded mutations in *LMNA* (lamin A/C) and *PPARG* (peroxisome proliferator activated receptor γ), a diagnosis of FPLD1 was made. A low-calorie diet was introduced, but glycemic control remained suboptimal despite large insulin doses. Triglyceride levels were modestly elevated (>2 mmol/L) (Table 1). Referral for gastric bypass surgery was made at the patient's request on clinical grounds at age 53. At this time, her body mass index (BMI) was 27.4 kg/m². Blood glucose readings fell within days of surgery, requiring the cessation of all medication (Supplemental Fig. 3), with a corresponding fall in hemoglobin A_{1c}. Oral glucose tolerance testing was undertaken before and 3 months after surgery (Fig. 1). Postoperatively, glucose tolerance was greatly improved, and this was associated

Table 1. Impact of RYGB on Anthropometric and Biochemical Measurements

	Patient A		Patient B			Patient C		Ref Range
	Preoperative	Postoperative 3 Months	Preoperative	Postoperative 3 Months	Postoperative 40 Months	Preoperative	Postoperative 18 Months	
BMI (kg/m ²)	27.4	21.7	32.4	24.7	26.8	29.7	22.9	
Body fat (%) ^a	49.1	42.9	37	24.5	NA	NA	28	
Android:gynoid ratio	1.46	1.28	1.53	1.38	NA	NA	1.16	
Fat mass ratio ^b	1.63	1.56	1.80	1.83	NA	NA	1.45	
Hepatic fat fraction (%) ^c	7	7	6	3	3.2	20	3.2	
HbA _{1c} (mmol/mol)	75	54	118	50	47	113	48	36–45
HbA _{1c} (%)	9.0	7.1	12.9	6.7	6.3	12.5	6.5	4.9–6.3
Leptin (ng/mL)	59.1	7.6	15.6	3	9.8	20.9	6.2	^d
Adiponectin (g/mL)	5.9	8	3.8	4.6	7.1	4.3	16.5	^e
Leptin/adiponectin ratio (ng/ μ g)	10.0	1.0	4.1	0.7	1.3	4.9	0.4	
Insulin (pmol/L)	67	18	67	35	29	132	33	0–80
C-peptide (pmol/L)	608	312	890	662	774	1897	1210	170–960
Cholesterol (mmol/L)	8.2	7.6	4.9	2.6	3.7	5.3	4.1	
Low-density lipoprotein (mmol/L)	6.3	5.5	3.4	1.4	1.8	2.6	1.8	
Triglyceride (mmol/L)	2	2.8	1.1	0.5	0.7	3.5	1.9	
High-density lipoprotein (mmol/L)	1.0	0.8	1.0	1.0	1.5	1.1	1.4	
Albumin (g/L)	37	34	38	38	37	38	35	35–50
Bilirubin (μ mol/L)	11	8	6	6	6	5	3	0–20
Alk phos (U/L)	106	111	126	72	47	132	96	30–130
Alanine aminotransferase (U/L)	18	18	27	32	26	51	22	7–40
GGT (U/L)	21	11	28	19	10	66	11	0–37
TSH (mU/L)	2.3	2.5	1.4	1	1.3	1.0	1.2	0.35–5.55
FT ₄ (pmol/L)	14.2	NA	15.8	12.8	11.5	15.3	10.8	10.0–19.8
Insulin dose (unit/d)	110–200	0	80–120	0	0	20–40	0	
Additional medical therapy	Telmisartan		Metformin Sitagliptin Simvastatin Ramipril	Metformin Simvastatin	Metformin Simvastatin	Metformin Gliclazide Liraglutide Losartan		

Abbreviations: Alk phos, alkaline phosphatase; FT₄, free T₄; GGT, gamma-glutamyl transferase; HbA_{1c}, hemoglobin A_{1c}; NA, not available; TSH, thyroid-stimulating hormone.

^aDEXA.

^bFat mass ratio represents percentage trunk fat compared with legs.

^cMagnetic resonance imaging.

^dLeptin ref range (ng/mL) (female): BMI 25 kg/m² = 2.5 to 24.4; BMI 25 to 30 kg/m² = 8.6 to 38.9; BMI 30 to 35 kg/m² = 14.9 to 60.9; BMI >35 kg/m² = 27.7 to 113.6.

^eAdiponectin ref range (μ g/mL) (female): BMI 25 kg/m² = 4.4 to 17.7; BMI 25 to 30 kg/m² = 3.5 to 15.5; BMI 30 to 35 kg/m² = 2.6 to 14.9; BMI >35 kg/m² = 2.6 to 17.1.

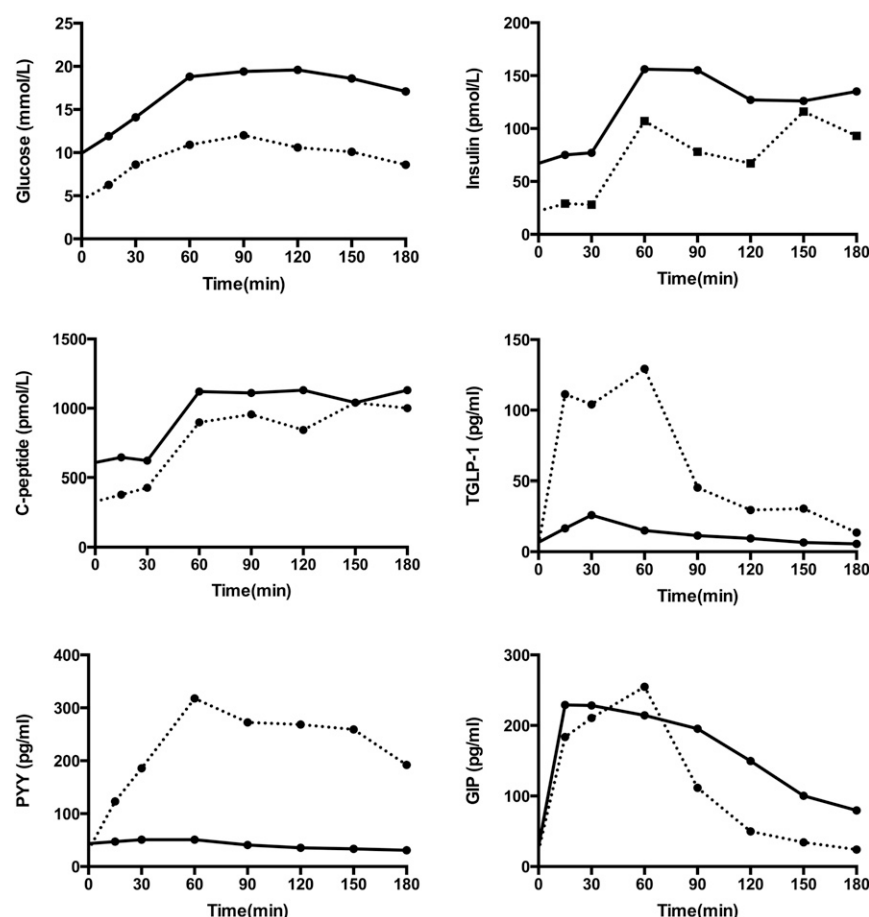


Figure 1. The pancreatic and enteroendocrine hormonal responses of patient A to a 50-g oral glucose tolerance test preoperatively (black line) and 3 months following RYGB surgery (dashed line). Glucose tolerance improved postoperatively. GLP-1 and PYY response to glucose load increased at 3 months, while glucose-dependent insulinotropic polypeptide was largely unchanged.

with dramatically increased L-cell-derived satiety hormones glucagonlike peptide-1 (GLP-1) and peptide YY (PYY). Glucose-dependent insulinotropic polypeptide levels were unchanged. Consistent with the reduction in adiposity and fasting glucose, fasting insulin levels were markedly reduced, whereas the incremental insulin response to the glucose load was similar to that found preoperatively, despite the much lower postprandial glucose levels.

Patients B and C

Two further female patients were diagnosed with FPLD1 following the exclusion of hypercortisolism and pathogenic *PPARG* variants. Both displayed the classical clinical features of FPLD1. Patient B had hypertension, dyslipidemia, NAFLD, and secondary diabetes requiring >180 units of insulin daily. She gained weight in parallel with increasing insulin doses. A structured weight management program achieved modest weight loss, but HbA_{1c} remained >100 mmol/mol (11.3%), and retinopathy and nephropathy had developed. Patient C also experienced NAFLD, dyslipidemia, and poorly

controlled diabetes despite multiple glucose-lowering therapies. She did respond favorably (weight loss of 4.6 kg and improved glycemic control) to a low-energy liquid diet but was unable to sustain the weight loss. Both patients were referred for Roux-en-Y gastric bypass (RYGB) surgery. Patient B was age 44 and obese with a BMI of 32.4 kg/m². Postoperatively, her insulin was stopped due to dramatic improvements in blood glucose, and she is currently well controlled on metformin alone. At age 53 with a BMI of 29.7 kg/m², patient C underwent gastric bypass surgery that resulted in a dramatic improvement in diabetes control and cessation of all glucose-lowering medication. In addition to weight loss, both patients experienced a reduction in hepatic fat and fasting insulin levels (Table 1). Patient B had an uncomplicated course and remains well 40 months post RYGB. Patient C developed a gastric ulcer at 18 months postoperatively and reported dental caries, but she too remains metabolically well.

Discussion

FPLD1 is a disorder characterized by reduced peripheral adipose tissue expandability (1). This is thought to engender a mismatch between the need and capacity to buffer excess energy intake leading to insulin resistance and its associated metabolic problems. The mainstay of therapy, although challenging to achieve, is reduced caloric intake (Supplemental Fig. 4) (2). Patients with FPLD1 who lose weight manifest significant metabolic improvements. However, they struggle to sustain this, perhaps in part due to relative leptin deficiency secondary to peripheral lipodystrophy. RYGB, previously viewed solely as a bariatric procedure, has emerged as effective therapy in the management of metabolic dysfunction in obese individuals, raising the question of its role in nonobese individuals with deranged glycemic control.

We assessed the impact of RYGB on fat mass in three patients with FPLD1; all manifested substantial sustained weight loss, and DEXA imaging demonstrated a reduction in fat across all body compartments. A marked decline in android fat mass was evident, owing to the pathological distribution of fat observed in FPLD1 (Fig. 2). Our patients reported reduced hunger

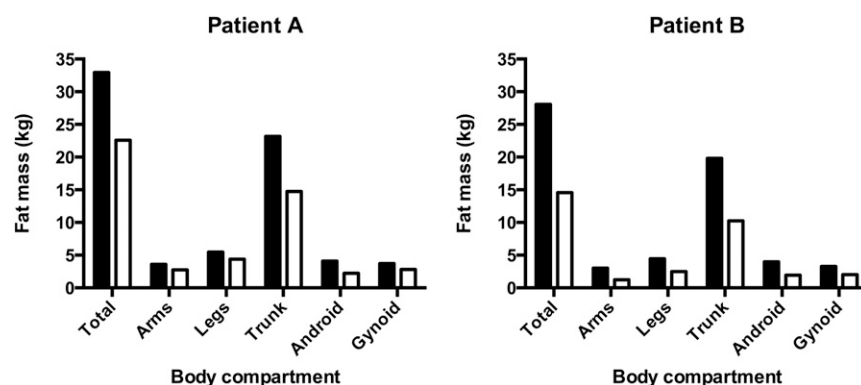


Figure 2. The changes in fat mass between the preoperative (black bars) and 3-month postoperative (white bars) periods in two patients with FPLD1 undergoing RYGB.

postoperatively, despite the postoperative drop in leptin levels, and it is likely that this is the primary reason for the beneficial impact of surgery on energy balance. The precise basis for the appetitive changes that occur post RYGB surgery in all patient groups is a topic of intense scientific activity, but the increased post-prandial levels of GLP-1 and PYY3 through PPY36, hormones with an anorectic effect, are likely to play an important role.

The most dramatic clinical impact in all three patients was on the poorly controlled type 2 diabetes that was present preoperatively. The improvement in glycemic control is consistent with that seen in obese individuals with type 2 diabetes who undergo bariatric surgery (4) or who sustain a period of negative energy balance due to intense dietary restriction (5). Patients with FPLD1 are frequently very insulin resistant, almost certainly due to lipotoxicity in insulin-responsive tissues such as muscle and liver, which are responsible for a large component of glucose clearance; this was reflected in the high insulin doses and poor glycemic control of patients A and B and in the high fasting insulin levels in patient C. Measures of insulin resistance (fasting insulin and leptin-adiponectin ratio) were markedly improved in all three patients postoperatively, likely due to the reduction in lipotoxic load to insulin-responsive tissues as a result of sustained negative energy balance. It is possible that the increased GLP-1 levels had an additional impact on glycemic control through their incretin effect, but the dramatically different fasting and post-load glucose levels that were present pre- and post-operatively in patient A make it impossible to comment meaningfully on this.

Patient A did not have a marked elevation in hepatic fat (at least as measured noninvasively) or in circulating triglycerides, but these measures were more markedly abnormal in patients B and C in whom the beneficial impact of surgery on liver fat and circulating lipids was more obvious.

All of our patients have remained clinically well at follow-up; however, patient C developed a gastric ulcer, which was treated effectively with medical therapy. Although serious adverse events are uncommon following metabolic procedures, patients should be counseled on the procedure risks and the requirement for extended follow-up and nutritional supplementation. To date, RYGB has been the only metabolic surgery reported in patients with lipodystrophy, and it is unknown if

similar efficacy would be seen with other weight-lowering procedures.

Conclusion

Reports of the use of RYGB in the management of lipodystrophy are sparse. In addition to one previously reported case in FPLD1, RYGB has been used in FPLD2 (LMNA) and FPLD4 [perlipin 1 (*PLIN1*)] monogenic lipodystrophies (6–10). In our FPLD1 cases, RYGB achieved glycemic targets where optimum medical therapy had been unsuccessful, additionally reducing ectopic fat deposition as a likely critical mediator of the metabolic dysregulation observed in this condition. RYGB may be an important adjunct to optimal medical management of patients with FPLD1.

Acknowledgments

We thank the patients for their willingness to participate in these studies and Laura Watson and the staff of the National Institute for Health Research/Wellcome Trust Clinical Research Facility for providing body composition analysis.

Financial Support: This work was supported by Wellcome Trust Grants WT106262, WT098498, WT095515, and WT107064 (to F.G., G.R., R.K.S., S.O., and D.B.S.), the Medical Research Council Metabolic Disease Unit, the National Institute for Health Research Cambridge Biomedical Research Centre, and the National Institute for Health Research Rare Disease Translational Research Collaboration.

Correspondence and Reprint Requests: Francesco Rubino, MD, Bariatric and Metabolic Surgery, Division of Diabetes and Nutritional Sciences, Kings College London, Denmark Hill Campus, 125 Coldharbour Road, London SE5 9NU, United Kingdom. E-mail: francesco.rubino@kcl.ac.uk; or Anna Stears, MD, University of Cambridge Metabolic Research Laboratories, Wellcome Trust-MRC Institute of Metabolic Science, Box 289, Addenbrooke's Hospital, Cambridge CB2 0QQ, United Kingdom. E-mail: anna.stears@addenbrookes.nhs.uk; or David B. Savage, MD, University of Cambridge Metabolic Research Laboratories, Wellcome Trust-Medical Research Council

Institute of Metabolic Science, Box 289, Addenbrooke's Hospital, Cambridge CB2 0QQ, United Kingdom. E-mail: db23@medschl.cam.ac.uk.

Disclosure Summary: The authors have nothing to disclose.

References

1. Garg A. Clinical review: Lipodystrophies: genetic and acquired body fat disorders. *J Clin Endocrinol Metab*. 2011;**96**(11):3313–3325.
2. Brown RJ, Araujo-Vilar D, Cheung PT, Dunger D, Garg A, Jack M, Mungai L, Oral EA, Patni N, Rother KI, von Schnurbein J, Sorkina E, Stanley T, Vigouroux C, Wabitsch M, Williams R, Yorifuji T. The diagnosis and management of lipodystrophy syndromes: a multi-society practice guideline. *J Clin Endocrinol Metab*. 2016;**101**(12):4500–4511.
3. Diker-Cohen T, Cochran E, Gorden P, Brown RJ. Partial and generalized lipodystrophy: comparison of baseline characteristics and response to metreleptin. *J Clin Endocrinol Metab*. 2015;**100**(5):1802–1810.
4. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, Navaneethan SD, Singh RP, Pothier CE, Nissen SE, Kashyap SR; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. *N Engl J Med*. 2017;**376**(7):641–651.
5. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia*. 2011;**54**(10):2506–2514.
6. Ciudin A, Baena-Fustegueras JA, Fort JM, Encabo G, Mesa J, Lecube A. Successful treatment for the Dunnigan-type familial partial lipodystrophy with Roux-en-Y gastric bypass. *Clin Endocrinol (Oxf)*. 2011;**75**(3):403–404.
7. Grundfest-Broniatowski S, Yan JL, Kroh M, Kilim H, Stephenson A. Successful treatment of an unusual case of FPLD2: the role of Roux-en-Y gastric bypass. Case report and literature review. *J Gastrointest Surg*. 2016;**1-5**: 10.1007/s11605-016-3300-2.
8. Kozusko K, Tsang V, Bottomley W, Cho YH, Gandotra S, Mimmack ML, Lim K, Isaac I, Patel S, Saudek V, O'Rahilly S, Srinivasan S, Greenfield JR, Barroso I, Campbell LV, Savage DB. Clinical and molecular characterization of a novel PLIN1 frameshift mutation identified in patients with familial partial lipodystrophy. *Diabetes*. 2015;**64**(1):299–310.
9. McGrath NM, Krishna G. Gastric bypass for insulin resistance due to lipodystrophy. *Obes Surg*. 2006;**16**(11):1542–1544.
10. Utzschneider KM, Trence DL. Effectiveness of gastric bypass surgery in a patient with familial partial lipodystrophy. *Diabetes Care*. 2006;**29**(6):1380–1382.